

What is the efficacy of switching to weekly pegvisomant in acromegaly patients well controlled on combination therapy?

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ABSTRACT

Context: While combination therapy of acromegaly with long-acting somatostatin analogues (LA-SSAs) and pegvisomant (PEGV) normalizes insulin-like growth factor-I (IGF1) levels in the majority of patients, it requires long-term adherence. Switching from combination therapy to monotherapy with weekly PEGV could improve patient comfort, but the efficacy is unknown.

Objective: to assess the efficacy of switching to PEGV monotherapy in patients well controlled on combination therapy of LA-SSAs and PEGV.

Design: Single center, open-label observational pilot study. LA-SSA therapy was discontinued at baseline and all patients were switched to PEGV monotherapy for 12 months. If IGF1 levels exceeded 1.0 times upper limit of normal (ULN), PEGV dose was increased by 20 mg weekly.

Subjects and methods: 15 subjects (8 males) were enrolled, with a median age of 58 years (range 35-80) on combination therapy of high-dose LA-SSAs and weekly PEGV for >6 months, and IGF1 levels within the normal range. Treatment efficacy was assessed by measuring serum IGF1.

Results: After 12 months of weekly PEGV monotherapy, 73% of the subjects' IGF1 levels remained controlled. In one patient LA-SSA had to be restarted, due to recurrence of headache. IGF1 levels increased from a baseline level of 0.62 x ULN (range 0.30-0.84) to 0.83 x ULN (0.30-1.75) after 12 months, while the median weekly PEGV dose increased from 60 (30-80) mg to 80 (50-120) mg.

Conclusion: Our results suggest that switching from combination therapy of LA-SSAs and PEGV to PEGV monotherapy can be a viable treatment option for acromegaly patients without compromising efficacy.

Introduction

Acromegaly is a rare disease characterized by somatic overgrowth and endocrine dysfunction due to excessive secretion of growth hormone (GH) and subsequent elevation of insulin like growth factor-I (IGF1) levels. In more than 90% of patients it is caused by a benign growth hormone-secreting pituitary adenoma (1). The main causes of death in acromegaly patients are cardiovascular and respiratory diseases (2, 3). Normalization of GH and IGF1 levels will result in normal mortality rates, reduced morbidity and a reduction in symptoms (3).

The growth hormone receptor antagonist pegvisomant (PEGV) is the medical treatment that has the highest reported efficacy (4). PEGV can be administered with or without long-acting somatostatin analogues (LA-SSAs) (5, 6). Administration of PEGV alone at a mean weekly dose of 130 mg can normalize IGF1 levels in over 90% of patients (7). If LA-SSAs and PEGV are used together, a similar efficacy of over 90% is achieved. However, a considerably lower mean weekly dose of 77-80 mg PEGV is required, this may result in a more cost-effective treatment.

Both LA-SSAs and PEGV are administered, respectively as intramuscular and subcutaneous injections. LA-SSAs are injected every four weeks, while PEGV can be injected either as a daily or as a weekly injection. While most studies on efficacy have been based on clinical trials that evaluated the daily injection (7, 8), only one study has assessed the weekly injection. Higham et al reported a normalization of IGF1 in 71% of acromegaly patients (n = 7) treated with weekly PEGV monotherapy (9).

Switching patients from combined therapy of LA-SSAs and PEGV to monotherapy with PEGV can reduce the total number of injections, and therefore improve patient adherence. In addition, PEGV monotherapy allows for easier dose adaptation.

In this pilot study, we assessed the effect of switching from combination therapy to weekly PEGV monotherapy. The main outcome parameters were the proportion of patients with normalized IGF1 levels after 12 months follow-up with weekly PEGV monotherapy.

SUBJECTS AND METHODS

Patients

In 2009, a prospective observational study enrolled 15 subjects (8 males) with acromegaly from a single centre, who were treated with a combination of LA-SSAs

Table 1: Baseline characteristics of all subjects (n = 15)

	N (%)
Demographics	
Sex, female	8 (53.3)
Age, median (range)	58 (35 - 80)
Diabetes mellitus type 2	3 (20)
Previous treatments	
Transsphenoidal surgery	3 (20)
Transsphenoidal surgery and radiotherapy	6 (40)
Primary medical therapy	6 (40)
Weekly PEGV dose (mg) - median (range)	60 (9.3 - 33.4)
Serum assessments	
IGF1 (nmol/L)	15.7 (9.3 - 33.4)
IGF1 x ULN	0.62 of ULN (0.30 - 0.84)
GH ($\mu\text{g/L}$)	3.03 (0.19 - 15.95)
Glucose (mmol/L)	5.4 (3.4 - 20)
HbA1c (mmol/L)	6.1 (5.1 - 9.2)
Long-acting somatostatin analogues	
Lanreotide Autogel	13 (87)
Octreotide LAR	2 (13)

(13 Lanreotide Autogel, 2 octreotide LAR) and PEGV (table 1). These patients received combination therapy because their serum IGF1 levels exceeded the normal range or because their acromegaly symptoms persisted during high dose of LA-SSA monotherapy (5). Inclusion criteria for the present study were a stable LA-SSA dose, the use of PEGV as a weekly injection and biochemical remission for over 6 months before enrolment, defined by an IGF1 within the normal range for sex and age of < 1.0 ULN (8). The cause of acromegaly needed to be a GH secreting pituitary adenoma and the allowed dose of weekly PEGV was ≤ 80 mg. The median age of the study group was 58 (range 35 - 80) years. Three patients had received surgery of the pituitary adenoma in the past, while 6 patients had been treated with both surgery and radiotherapy. Radiotherapy was administered at least 5 years before study entry. Six patients had only received medical treatment. Three patients had diabetes and were using oral medication, while one diabetes patient also used insulin. All patients gave their written informed consent, and the study was approved by our local IRB.

One patient had to be restarted with LA-SSAs during the study period due to a recurrence of symptoms and therefore did not want to continue with the PEGV alone. This patient was reported as uncontrolled and was censored from the results after withdrawal, but was counted as treatment failure.

Study

At the start of the study LA-SSAs were discontinued for 12 months and only PEGV was continued. Every 6 weeks patients visited our outpatient clinic for measurements of IGF1 levels, HbA1c, glucose, insulin, cholesterol, free fatty acids (FFA), and triglycerides. During the visits, data on symptoms and safety assessments were collected and the dose of PEGV was adjusted if necessary. IGF1 levels were measured by immunometric assays (Diagnostic Products Corp., Los Angeles, CA) and were interpreted according to the sex and age dependent ranges (10). GH and serum PEGV levels were measured at the start of the trial, after 6 months and after 12 months. Since endogenous GH was in the presence of PEGV, GH levels were measured using a specific assay free of interference of the drug (11). When IGF1 levels exceeded the normal range, the PEGV dose was further increased by 20 milligrams per week. This was continued until the IGF1 levels were within the normal range for sex and age and PEGV dose was not changed. Doses were divided into two equal portions per week when PEGV exceeded 80 mg. Efficacy of PEGV monotherapy was assessed 12 months after discontinuation of the combination therapy. Safety assessment included measurement of serum alkaline phosphatase, γ -glutamyl transpeptidase (γ -GT), alanine aminotransferase (ALT), aspartate aminotransaminase (AST), lactate dehydrogenase and total bilirubin. A pituitary MRI was performed before study entry and after the study.

Statistics

Prism version 5.00 for windows (Graphpad Software, San Diego CA) was used for the statistical analyses of the data. Although the nature of the study was mainly descriptive, pertinent data were analysed by Wilcoxon's signed-rank test. Statistical significance was defined by $P < 0.05$ (two-tailed). Data are expressed as median \pm (range), unless specified otherwise.

RESULTS

Efficacy

Fifteen patients were enrolled in this study. At baseline the IGF1 levels of all patients were controlled with a median IGF1 level of 62% of the upper limit of normal (ULN) (range 30 % to 84 %), (figure 1).

At 6 months, IGF1 levels started to increase to 100% of the ULN (range 43-220%). The slow increase of IGF1 started 12 weeks after cessation of the LA-SSA. At baseline, patients were using PEGV at a median dose of 60 mg (range 30-80 mg).

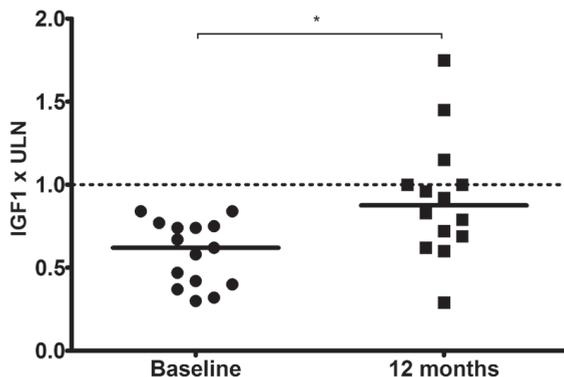


Figure 1. IGF1 levels at baseline and after 12 months of pegvisomant therapy. IGF1 levels expressed as times upper limit of normal, at baseline (n = 15) and after 12 months (n = 14). One patient restarted somatostatin analogues due to recurrence of symptoms.

After 12 months, median IGF1 levels increased to 83% (30-175%) of the ULN ($P < 0.05$) (figure 1). The median PEGV dose had been increased to 80 mg (50 - 120 mg) ($P < 0.05$). IGF1 remained controlled in 11 of 15 subjects (73 %) after 12 months of weekly PEGV monotherapy.

At the start of the study median serum PEGV levels were 3.00 mg/L (0.25 - 19.44). After an initial decrease in serum PEGV levels 2.23 (0.44 - 12.10) at 6 months, PEGV levels increased to 4.36 mg/L (range 1.12 - 21.28) at 12 months. Between 6 and 12 months the serum PEGV levels were significantly higher ($p = 0.01$), but no difference was found between baseline and 6 or 12 months.

We compared PEGV levels between the subjects in whom IGF1 levels were elevated and those who had levels that remained within the normal range after 12 months. We observed that after 12 months, acromegaly patients with an elevated IGF1 tended to have lower PEGV levels, this was 3.85 mg/L (1.30 - 4.39 mg/L) in non-controlled patients compared with 5.54 mg/L (1.12 - 21.28 mg/L) in controlled patients ($p = 0.25$). Weekly PEGV doses and increases in doses were not different between controlled and non-controlled patients: the baseline median PEGV dose was respectively 60 (30 - 80 mg) in controlled versus 60 (40 - 80 mg) in non-controlled patients. After 12 months the respective median PEGV dose increased to 80 (50 - 120 mg) in controlled versus 100 (80 - 120 mg) in non-controlled patients. The median increase in PEGV dose was +10 (0 - 60 mg) in those who were controlled after 12 months, while this was +40 (20 - 40 mg) for those who were non-controlled.

Five subjects did not require changes in PEGV dosing, since their IGF1 level remained within the age adjusted normal limits. All 5 had received combination therapy longer (5.88 (2.26 - 6.01) years) than the other 10 subjects (2.52 (1.48 - 6.39) years).

Over time the GH levels tended to increase during PEGV monotherapy. At baseline we measured 2.99 µg/L (range 0.19 - 15.95 µg/L) compared with 3.22 µg/L (0.12 - 79.14) at 6 months, and 6.36 µg/L (range 0.180 - 31.45 µg/L) at 12 months. The GH levels at baseline, 6 months and 12 months were significantly different ($p < 0.05$), except for baseline vs. 12 months ($p = 0.055$).

Safety

No significant safety issues were observed during PEGV monotherapy. After 12 months glycosylated haemoglobin (HbA1c) decreased significantly from 6.0 % (5.1 - 9.2 %) to 5.9 % (5.0 - 9.1 %) ($p = 0.02$). The patients with diabetes had no alterations to their anti-diabetic medication during the study. No significant elevation of liver enzymes was observed and the pituitary MR did not show any change in tumour-size. The one patient who withdrew from the study had severe headaches that resolved after reinitiating LA-SSAs.

DISCUSSION

In this study we followed 15 acromegaly patients who previously were biochemically controlled with LA-SSAs and weekly PEGV. These patients had been switched to combination therapy since their IGF1 levels could not be controlled by LA-SSA monotherapy. In this study, we discontinued LA-SSAs and continued with weekly PEGV monotherapy. At baseline, 100% of the subjects had IGF1 levels within the normal limits during combination therapy. After 12 months follow-up 73% remained controlled.

The efficacy of 73% is in the same range as the efficacy of 68% reported by the ACROSTUDY group. However, we achieved this proportion of IGF1 normalization at a median PEGV dose of 80 mg/week after 12 months, whereas the ACROSTUDY group reported this at a median PEGV dose of 17.2 mg/day after 5 years, which corresponds to approximately 120 mg/week(12). The subjects enrolled in our study used relatively low doses of PEGV and had used the combination with LA-SSAs for at least 1.5 years. Since this may have had an impact on our results, these results cannot be extrapolated to all patients using combination therapy.

The slow and gradual increase in serum IGF1 levels that we observed sixteen weeks after discontinuation of LA-SSAs is in line with the expected wash-out time of the LA-SSAs and the carry-over effect of the LA-SSAs of about 15-20 weeks(5, 13, 14). During 12 months of follow-up five of 15 patients did not need any dose adaptation. Although IGF1 levels also increased in these patients, they remained within the age-adjusted normal range. Combination therapy in these 5 patients lasted for longer, than for the other patients in the study. A longer period of treatment with LA-SSA might result in prolonged “suppression” of GH, which may improve the efficacy of PEGV, a competitive inhibitor of the GH receptor(4). In the total population, single measurements of GH tended to increase at 6 and 12 months during the study. However, subjects in whom IGF1 remained within the normal range tended to have lower GH levels than those with elevated IGF1 levels.

Subjects in whom IGF1 levels increased after the discontinuation of the LA-SSAs tended to have lower PEGV serum levels, despite treatment with similar doses of PEGV. One would expect that PEGV levels would decrease after discontinuation of LA-SSAs, since LA-SSAs increase the PEGV serum levels by approximately 20% compared with an identical dose of PEGV alone(6, 11). This observation explains the difference in PEGV levels between controlled and uncontrolled patients at 6 months, but not the difference in PEGV levels at 12 months. A potential explanation is that uncontrolled patients do not increase in PEGV serum levels as much as controlled patients when the weekly dose of PEV is increased. The large difference in serum PEGV levels between subjects has been reported before(15).

Possibly due to the small sample size of our study however, we found no association between PEGV dose and previously reported characteristics such as adiposity and body weight.

The one patient who was discussed in the safety analysis was withdrawn from the study because she suffered from severe headaches, even though IGF1 was controlled (98% of ULN). After recommencing LA-SSA co-treatment the headache disappeared. The pituitary MRI scan showed no explanation for the headache. In this specific case, we suspect that there was a causal relationship between discontinuation of LA-SSA and the headache. As expected, HbA1c levels decreased significantly in these patients in our study. However, the change was very small, and therefore of dubious clinical relevance.

This was a pilot study on monotherapy with weekly PEGV to assess whether ceasing LA-SSAs is a viable option in a selection of our patients on combination therapy.

A drawback of this pilot is the small sample size. Nevertheless, our results suggest that a significant number of acromegaly patients on low-dose PEGV in combination with LA-SSAs can temporarily stop their LA-SSA treatment for at least a year. These treatment interruptions may improve patient adherence to the medication and reduce the economic burden of long-term use of expensive medications.

We conclude that discontinuing LA-SSAs and continuing with PEGV may be an interesting alternative for a selected group of patients that are well-controlled with a combination of LA-SSAs and relatively low-doses of PEGV. It is possible to maintain biochemical control up to 12 months in a substantial number of patients without raising the dose of PEGV. In patients who have previously been treated for an extended time with LA-SSAs, there is no need to adjust therapy even after 12 months. It seems sensible to determine the usability of structured interruptions in medical therapy in patients with acromegaly in a larger study.

Declaration of interest

A.J. van der Lely is consultant for Novartis Pharma, Pfizer International and received grants from Novartis Pharma, Ipsen Pharma International and Pfizer International. SN received research grant from Ipsen and Pfizer. JOLJ is a consultant for Pfizer and Novartis and has received lecture fees and unrestricted research grants from Novartis, Pfizer and IPSEN. The other authors have nothing to disclose.

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